# APPENDIX Z

## Wyeth's Grounds for Appeal filed August 1, 2005

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Wyeth



SKM/es
1 August 2005

**BY FACSIMILE**

The European Patent Office
D-80298
**MUNCHEN**
Germany

CONFIRMATION

Dear Sirs, 96915746.0

**Grounds of Appeal in the matter of European Patent No. 830142**
**Proprietor: Boehringer Ingelheim Vetmedica Inc.**
**Opponent : Wyeth**
**Our Ref : SM-1284**

Wyeth hereby files Grounds of Appeal against the Decision of the Opposition Division in respect of EP 830142/01 dated 22 March 2005.

The Decision is appealed for the reasons and supporting documents set forth in Annex 1 hereto. We request the file history of the Examination and Opposition is made available to this Appeal. The file history is easily accessible to all parties and therefore we do not file a copy herewith. In Annex 1 we have identified the additional documents on which we intend to rely. All of the documents are available in the public domain so for the purpose of filing the Grounds of Appeal by fax we have enclosed only D6 and D7 along with enlarged pages and confirmation of publication dates, and D12. A copy of all the documents relied on will be sent with the confirmation copy of this letter with a separate copy direct to the Patentee.

The Opponent maintains its original request that the Patent is revoked in its entirety. An oral hearing is requested if the Appeal Board considers maintaining the Patent in any form. A form 1037 accompanies the confirmatory copy of this fax letter for acknowledging receipt.

Yours faithfully

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# Wyeth

1st August 2005
SKM/lb

**BY COURIER**

Keller, Günter, Dr., et al
Lederer & Keller Patentanwälte
Prinzregentenstrasse 16
80538 München
Germany

Dear Sirs,

**RE: APPEAL BY WYETH**
**AGAINST EUROPEAN PATENT NO. 0 830 142 (filing date 14 May 1996)**
**OUR REF : SM-1284**

Please find enclosed one copy of our Appeal regarding the above-mentioned patent as filed today.

Yours faithfully

S K Mannion (Dr)
European Patent Attorney

Encs.

ANNEX 1

**OPPOSITION:** **EUROPEAN PATENT NO. 830 142**
**EUROPEAN APPLICATION NO. 96915746.0**
**FILED:** **14 May 1996**
**PROPRIETOR:** **Boehringer ingelheim Corporation**
**OPPONENT:** **Wyeth**

## GROUNDS OF APPEAL

**The Opponent/Appellant maintains the request that the European Patent No. 830 142 (the Patent) is revoked in its entirety on the ground of Article 100(a) EPC that the subject matter of the Patent as granted and as maintained by the Opposition Division by their written decision of March 22, 2005, lacks novelty and inventive step.**

### 1. Document List

D1 EP 529584 A2

D2 Yuan et al. "Complete genome comparison of porcine reproductive and respiratory syndrome virus parental an attenuated strains." Virus Research 74 (2001) 99-110.

D3 Yuan et al. Erratum to "Complete genome comparison of porcine reproductive and respiratory syndrome virus parental an attenuated strains". Virus Research 79 (2001) 189-200.

D4 Murtaugh et al. "Genetic variation and biological safety of Ingelvac MLV modified live PRRS Vaccine during seven years of continuous use in the field." 4th International Symposium on Emerging and Re-emerging Pig Diseases. Rome, June 29th –July 2nd, 2003.

D5 J. Christopher-Hennings et al, "Effects of a modified-live virus vaccine against porcine reproductive and respiratory syndrome in boars," AJVR, Vol. 58 No. 1 January 1997.

D6 Gorcyca et al. "ResPRRS: A New Tool for the Prevention and Control of PRRS in Pigs." 26th Annual Meeting of American Association of Swine Practitioners, March 4-7,1995.

D7 Nobl Laboratories Inc. "A New Tool in the Fight Against PRRS. RespPRRS®." 1994 (and enlarged copy of date and RespPRRS® pack)

D8 Nielsen et al. "Examination of virus shedding in semen from vaccinated and from previously infected boars after experimental challenge with porcine reproductive and respiratory syndrome virus." Veterinary Microbiology, 54 (1997) 101-112.

D9 Bøtner et al., "Appearance of acute PRRSV-like symptoms in sow herds after vaccination with a modified live PRRS vaccine," Veterinary Record (1997) 141, pp. 497-499.

D10 W.L. Mengeling et al. "Attenuation of Porcine Reproductive and Respiratory Syndrome Virus by Serial Passage in Cell Culture." Proceedings of the 14th IPVS Congress, Bologna, Italy, 7-10 July 1996, page 64.

D11 Mortensen et al., "Adverse Effects of the Ingelvac™ PRRSV Modified Live Vaccine on Sow Productivity in Herds infected with Porcine Reproductive and Respiratory Syndrome Virus." Proceedings of the 15th IPVS Congress, Birmingham, England, 5-9 July 1998, p.128.

D12 Translation of Extract from the Records of the Danish Eastern High Court. Judgment delivered on 4th February 2005. Available from the internet web-site of Landsudvalget for Svin at the following address: http://www.danskeslagterier.dk/smcms/Landsudvalget_Svin/Videnscenter/Faglige_temaer/PRRS-dommen/engelsk/Index.htm?ID=8173

D13 Torrison et al., "Evidence of Pig-to-Pig Transmission of a Modified-Live PRRS Virus Vaccine." American Association of Swine Practitioners, , Nashville, US, March 4-7,1996 pp. 89-91.

D14 WO94/18311

D15 WO93/07898

D16 Michael Murtaugh. The PRRS Virus. 1993 Allen D. Lemain Swine Conference.

## 2. The Contested Decision

By virtue of the decision dated 22 March 2005, the Opposition Division maintained the Patent on the basis of the Auxiliary Request 1 filed at the Oral Hearing which contains Claims 1-9, drawn to a method of producing a PRRS vaccine in which the PRRS virus, ATCC-VR2332 is passaged at least 70 times in cell culture of monkey

kidney cell line MA-104 to achieve attenuation of the virus. A stabilizer is added to harvested virus and the product is lyophilized.

The corresponding vaccine composition claims were revoked by the Opposition Division for the reason that the vaccines according to these claims are not capable of being distinguished from the prior art. In practice, the features of Claim 1 as originally granted, i.e., "modified and substantially avirulent", and "fails to cause clinical signs of PRRS disease but is capable of inducing an immune response" are features which are present in the prior art, and therefore are not capable of distinguishing the claimed vaccine from the prior art. The Opposition Division decided that the number of passages that a virus has under gone does not render the vaccine virus claims novel and it also does not reproducibly provide any other inherent feature which would distinguish it from the art. The Patentee argued that the absence of shedding was an inherent feature of a PRRS virus having been passaged at least 70 times, however, the Opposition Division disagreed on the basis that it was unlikely that all culturing experiments in which the PRRS virus is passaged 70 times would lead to a virus which does not shed.

On the other hand, the Opposition Division decided that the method of producing the PRRS vaccine was capable of being distinguished over the prior art by virtue of including a stabilizer and being in a lyophilized form. While these features conferred novelty on the claims over D1, the Opposition Division decided that these features routine methods for producing vaccines. This meant the inventive step discussion was concerned with the feature of "passaging at least 70 times". At this point, the Opposition Division, to be consistent with the novelty approach to the vaccine claims, reformulated the problem so that method provided the possibility of a vaccine virus which does not shed. The Opposition Division decided that the skilled man would not be motivated to investigate further passaging to eliminate shedding or, even to provide a virus with improved attenuation.

The Opposition Division's decision to maintain the claims of the Auxiliary Request 1 is based on construction of a problem which has no basis in the Patent or closest prior art and based on an important misrepresentation by the Patentee regarding the solution to the adopted problem.

## 3. Article 54 EPC: Novelty

Since the identification of Prof. Michael Murtaugh as the expert for the Patentee shortly before the Oral Hearing, we have conducted a search of his numerous papers on the subject of PRRS viruses going back to earlier than the priority date of the Patent. Through a relatively recent paper on which Prof. Murtaugh is an author, it has come to our attention that the product RespPRRS® vaccine, a modified live vaccine of ATCC VR2332, falls within the scope of original Claim 1 as granted and was manufactured according to the method of Claim 1 of Auxiliary Request 1 (Claim 5 as originally granted).

We understand that the Patentee is appealing the decision of the Opposition Division with respect to Claims 1 to 4 of the Patent as granted. This novelty attack is equally relevant to the revoked claims, and we ask that due consideration be given to this argument during any reconsideration of the originally granted vaccine composition claims.

**The lack of novelty objection is established through pre and post published papers. These papers establish that RespPRRS® was commercially available for nearly a year before the priority date of the Patent.**

We enclose D7 which is a leaflet distributed by Nobl Laboratories, Inc. The leaflet describes the RespPRRS® vaccine and contains an abbreviated questions and answers section. The leaflet is dated at the bottom of the last page with "6/94" (see enlarged copy) indicating that the leaflet is dated June 1994. This date closely coincides with the registration of this product in the United States in July 1994. As evidence for the commercial availability of RespPRRS® in 1994, the leaflet is corroborated by further documents discussed below.

The RespPRRS® was sold in a lyophilized form as demonstrated by the words "Rehydrate with 100ml" in the top right hand corner of the box in the photograph (see the enlarged copy). Lyophilized products have to contain a stabilizer in order to ensure that they meet regulatory standards for shelf life (see, for instance, D15, page 8, first full paragraph).

The product documentation itself does not disclose the route of attenuation of the virus from which the vaccine is made, but as a result of our search we found such a disclosure in a journal reference on which Prof. Murtaugh is named as an author. D2 and D3 (which should be read together) disclose that RespPRRS® vaccine virus strain was attenuated by passaging at least 70 times, see the last paragraph of Section 3.1, wherein it is stated that "*RespPRRS® has developed individual genomes of variable nucleotide sequence due to strain evolution over the course of more than 70 passages*". Further, Section 4, in the second sentence of the first paragraph (page 108), states that RespPRRS® was attenuated "*during 70 passages in MA-104 cells.*" In Section 3.6, Prof. Murtaugh states that the RespPRRS® vaccine strain was released in 1994. Therefore, Prof. Murtaugh discloses in D2/D3 that the product of the method disclosed in Claim 1 was available to the public as RespPRRS® vaccine in 1994. The availability of the RespPRRS® vaccine before the priority date of this patent is further confirmed in other documents described below.

D6 is a copy of a paper given by employees of the Patentee at a symposium in March 1995, prior to the priority date of the Patent. The full paper was published in Proceedings that were given to attendees on March 4th, 1995. D6 describes field studies using RespPRRS® vaccine conducted before the priority date of the Patent.

Prof. Murtuagh is an author on another paper D4 which discloses that live, attenuated PRRS vaccine, Ingelvac PRRS MLV was administered to pigs in March and April 1995, and additional doses were used in May through July 1995. Ingelvac PRRS MLV is another tradename for RespPRRS® as noted by the citation at lines 5-7 of page 138, column 2, i.e., "(8)" which is D3, which we have already demonstrated discloses RespPRRS® vaccine virus as having been passaged 70 times in MA-104 cells.

D5 discloses that in "*July 1994, a modified live virus vaccine[b] was licensed for use in 3-18 week old pigs.*" Footnote b (found at the bottom of page 44) indicates that the vaccine was RespPRRS MLV vaccine.

G 1/92 establishes that the chemical composition of a product is state of the art when the product as such is available to the public and can be analysed and reproduced

by the skilled person, irrespective of whether or not particular reasons can be identified for analysing the composition.

It is clear from D2/D3 that the number of nucleotide changes in RespPRRS® is considered to define the level of attenuation. Before the priority date of the invention the skilled man was able to determine the nucleotide sequence of the RespPRRS® vaccine virus strain using routine methods methods involving the retrieval of the vaccine virus from the RespPRRS® product and standard sequencing thereof (D16). By determining the nucleotide changes, the skilled man could reproduce the mutations observed by routine methods well-known in the art, such as passaging or recombinant techniques. According to the authors of D2/D3, 41/44 nucleotide mutations were observed and VR-2332 is relatively stable when passaged alone in cell culture (see "Discussion," first paragraph, page 108). Thus, before the priority date of the Patent, the skilled man had access to the RespPRRS® vaccine of original Claim 1 as granted and was able to determine the attenuating mutations and repeat the method of Claim 1 of Auxiliary Request 1 to provide the vaccine.

Therefore, the claims as granted and as maintained at the Opposition Hearing lack novelty over the commercialization of RespPRRS® vaccine before the priority date of the Patent.

The Opponent agrees with the Opposition Division's decision regarding the vaccine composition claims as granted lacking novelty over D1. However, it now turns out that these claims lack novelty over the availability of the RespPRRS® product and the release of the vaccine virus and its mutations which are associated with the ATCC VR2332 virus passaged 70 times in MA-104 cells.

For the reasons given above, neither the vaccine described in Claim 1 as granted, nor the method of Claim 1 of the Auxiliary Request 1, were novel at the priority date of the Patent.

## 4. Article 56 EPC: Inventive Step

With respect to the method claims of Auxiliary Request 1, the Opposition Division allowed the Patentee to reformulate the problem which was characterized as follows

*"the technical problem objectively solved by the claimed method must be formulated as the provision of a method, with which it is possible to obtain viruses that do not shed when administered intramuscularly".* [emphasis added]

The Problem Solution approach is well known and set out below are the four stages:

(a) identifying the closest prior art

(b) assessing the technical results or (effects) achieved by the claimed invention when compared with the "closest state of the art" established

(c) defining the technical problem to be solved as the object of the invention to achieve these results, and

(d) examining whether or not a skilled person, having regard to the state of the art, would have suggested the claimed technical features for obtaining the results achieved by the claimed invention.

Moreover extracts from the Case Law of the Boards of Appeal of the European Patent Office, 4th Ed 2001 state:

page 106

**Rule 27(1)(c) EPC stipulates that an applications description must "disclose the invention as claimed in such terms that the technical problem (even if not expressly stated as such) and its solution can be understood, and state any advantageous effect of the invention with reference to the background art"**

page 106

**In identifying the problem it is not permissible to draw on knowledge acquired only after the date of filing or priority.**

page 107

**Inventive step had to be assessed on the basis of the skilled person's knowledge before the priority or filing date**

page 108

**"reformulation of the problem could be allowed "provided the skilled man could recognise the same as implied or related to the problem initially suggested"**

The Opponent disagrees with the Opposition Division's rationale for reformulating the problem. In addition, in order to apply the problem solution approach, the problem over the closest prior art must have been solved in order to then go on to determine

whether the solution is obvious. In the present case, the problem is not solved by the vaccine virus obtained by the method set out in the claims of Auxiliary Request 1.

With respect to the reformulation of the problem, the only mention of shedding in the Patent was in the very last paragraph of the description [0110] which stated "*The VR-2332 virus was also cold –adapted in parallel with the attenuation described in Example 1. This was done in order to develop a vaccine strain that prevented shedding of the virus by infected animals. Such cold adaptation was carried out by successive passages at a temperature of 31-35°C.*" The Opposition Division accepted that this disclosure did not support an amendment to the claim to state that the vaccine virus passaged at least 70 times did not shed, however, they considered that the skilled man would have understood from [0110] that elimination of shedding was desirable even though cold-passaging had been the only means of solving that problem disclosed in the description. This must be wrong.

There is no disclosure whatsoever in the Patent that it is desirable as an objective to eliminate shedding. The skilled man knows that shedding of a sufficiently attenuated virus is not a danger to the population. In the Patent, shedding is only mentioned in relation to an additional optional method for obtaining the vaccine virus, without any indication of how many passages at cold temperatures would be required to achieve lack of shedding of the virus. If shedding had been seen as a potential problem requiring a solution, much more information would have been provided with respect to how to eliminate shedding. Furthermore, the claims of the Auxiliary request do not require any cold adaptation, and therefore according to the Patent and to the Opposition Division's approach to novelty (i.e., the lack of predictability of the genetic mutations which arise during passaging), the claimed method cannot reproducibly provide a virus which does not shed. The Opposition Division dealt with this point by reformulating the problem so that it only had to be possible for the method to produce a virus that didn't shed.

It should be noted here that many attenuated MLV viral vaccines "shed" or pass the vaccine virus to non-vaccinated animals with whom they come in contact. However, shedding is only a problem when the vaccine virus causes disease in those non-vaccinated animals. So it is not an essential characteristic of a useful vaccine to be "non-shedding". Since MLV vaccines have the ability to replicate in the vaccinated

animal, a stronger immune response can result. Nonetheless, the MLV vaccine should not cause clinical signs of disease, whether in vaccinated animals or non-vaccinated animals which come into contact with the vaccinated animals.

We believe the Opposition Division was prepared to accept the reformulated problem in view of the declaration submitted by Prof. Murtaugh. In this Declaration, the results of some trials were presented which did not detect shedding in contact control pigs which had been in contact with pigs vaccinated intramuscularly with passage 70 VR-2332.

However, intramuscular application of the vaccine was neither a limitation of the claims, nor was it a preferred route of administration according to the Patent. In fact the preferred route of administration in the Patent is given in the second sentence of paragraph [0012] as "*local (upper mucosal) route or parenteral route of vaccination*". There is no justification for the Opposition Division to introduce the feature of intramuscular vaccination into the problem sought to be solved over the art.

Therefore, the problem was constructed without it having been indicated as a problem in the Patent, and further, without any reference to the closest prior art. The problem has been constructed also to allow for the fact that the Opposition Division did not believe that the 70+ passaging technique disclosed in the Patent reliably provided a vaccine virus which did not shed. It only had to be possible.

In any case, this problem was not solved because it is well established that the RespPRRS®, Inglevac MLV vaccine virus does shed with negative consequences for herds as described in the enclosed documents discussed below despite the early literature published by Patentee to the contrary. This means that the problem must be reformulated in view of the closest prior art.

Moreover, we agree with the Opposition Division that obviousness centered on the feature "passaging at least 70 times" and we maintain in this Appeal for the reasons given below that it was entirely obvious to the skilled man to continue passaging until the level of attenuation reached provided the desired improved features.

4.1 The problem of shedding was not solved by VR-2332 which had been subjected to 70+ passages in MA-104 cells.

D5 discloses the results of a study conducted in the United States where 2ml doses of the RespPRRS® vaccine given intramuscularly to each of 5 boars resulted in shedding of the vaccine virus in all the boars, see page 44, last paragraph (left-hand column) where it states "*In conclusion, the vaccine virus was shed in semen of breeding age boars, usually within the first 2 to 3 weeks after inoculation*".

In D8, the authors report results from a vaccination program in Denmark where in boars vaccinated intramuscularly with the live attenuated PRRS-vaccine "Ingelvac PRRS MLV, RespPRRS" the vaccine virus was detected in semen samples collected 2 weeks after vaccination.

D9 is another document from yet a different group of investigators in Denmark which reports shedding via semen of boars vaccinated with Ingelvac PRRS vaccine. On page 497, the authors explain the later introduction of the vaccine Ingelvac PRRS modified live virus vaccine in Denmark. On page 498, second column, 2nd full paragraph, the authors note that the spread of the vaccine virus with semen from boars in artificial insemination centres was demonstrated immediately after the introduction of the vaccine to Danish herds.

D11 is a still further document from yet another group of investigators in Denmark which in the "Discussion" (right-hand column) explains that "*Ingelvac™ PRRS had significant adverse effects on productivity in PRRS seropositive sow herds*" and attributed this to spreading of the vaccine strain to sows.

Still another paper which looked at the possibility of shedding by a MLV PRRS vaccine (RespPRRS® ) is D13 which found that "*virus transmission presumed to have originated from administration of a MLV PRRS vaccine an measured by seroconversion on the PRRS ELISA was observed in all pens.*" (see "Conclusions", page 90, first sentence)

Despite the statements submitted to the Opposition Division, Prof. Murtaugh, has elsewhere indicated that the Ingelvac MLV modified live vaccine virus sheds. Prof. Murtaugh is the lead author of D4 reporting on the genetic variation and biological safety of Ingelvac MLV modified live virus vaccine following more than seven years of continuous use in a field situation free of wild-type PRRS. Prof. Murtaugh notes

that Ingelvac PRRS MLV was administered to nonpregnant sows in March and April 1995, a further 93 doses were administered in May to July 1995. The main observation is that the vaccine virus has been mutating by passaging through the herd. This means that the vaccine virus has been shedding from one generation to the next generation of pigs. It states on page 137, second column, lines 8-9 that "*A recent isolate from November 2002, differs at 23 bases and is 3.8% different from vaccine.*"

The last sentence of D4 concludes that "*the large amounts of genetic variation present in PRRSV populations worldwide combined with the potential of attenuated PRRS vaccines to* ***spread vertically and horizontally in swine populations*** *indicates that the potential exists for the derivation and establishment of variants in the field from vaccine viruses.*" [emphasis added]. This is an explicit admission that the vaccine referred to in D2/D3 which has been passaged 70 times in MA-104 cells does shed the vaccine virus, since shedding is necessary for there to be horizontal spread.

All of these articles provide scientific evidence and documentation of instances where the spread of the disease in vaccinated herds is understood to be caused by the introduction of American-type PRRSV in both Europe and North America due to the spread of vaccine virus from Patentee's 70-passage VR-2332 vaccine product (RespPRRS®, Ingelvac MLV).

Further, earlier this year the Patentee was fined approximately 3.2 M Euros in Denmark for the damage resultant from spreading of the vaccine virus through the use of the Patentee's vaccine (D12). The Court found that the vaccine did not provide the safety one is entitled to expect and that the vaccine virus was either transmitted in semen or was airborne. Additional cases are still pending. Further the Danish court absolved the Danish Medicines Agency of liability because "Boehringer made an error by not notifying it of the known risks, especially the reproductive problems in Canada in the late autumn and during the winter of 1995-1996. "

Therefore, not only has the problem of shedding not been overcome with VR-2332 passaged at least 70 times, this vaccine virus has retained or reverted to virulency in the field. As a result it also does not meet the criteria set out originally in Claim 1 as

granted, i.e., it does not meet the criteria of "fails to cause clinical signs of PRRS disease."

4.2 The claims of the Patent and Auxiliary Request 1 lack inventive step

D1 remains the closest prior art.

The Opposition Division came to the conclusion that the claims of Auxiliary Request 1 are inventive over D1 because D1 did not mention shedding of PRRS as a problem and because the known solution to shedding was cold-adaptation, it would not be obvious to extend the number of passages in order to obtain a virus which did not shed. Thus it was argued that the skilled man would not see shedding as a problem and therefore would not be motivated to increase the number of passages to solve the technical problem identified to be solved.

However, this interpretation of D1 is contrary to the Opposition Division's interpretation of the teaching of the Patent when arriving at the problem to be solved. There was no indication whatsoever that the Patent set out to overcome a problem of shedding, only to improve the clinical features of the vaccine virus. In paragraph [0007] it states "*there is a real need in the art for an effective vaccine which can eliminate or at least ameliorate the effects of PRRS.*" Therefore, applying the same reasoning, the skilled man did not have to recognize shedding as a problem with the attenuated virus of D1 in order to be motivated to improve the attenuation of the vaccine virus to achieve better clinical features.

The Opposition Division equally did not consider the skilled man would be motivated in view of D1 to improve the clinical features by further attenuation by further passaging. It is not exactly surprising that D1 doesn't disclose the fact that the virus disclosed is not perfectly attenuated given that a patent was being sought. However, in the problem solution approach there is no requirement for there to be a recognizable problem disclosed in the closest prior art, the problem is formulated in view of the closest prior art in the same way as with chemical inventions. The problem over D1 is therefore, to provide an improved vaccine virus. The Patentee said the improvement was in the efficacy of the vaccine virus.

The question to be asked is whether further passaging over the example of D1 would be obvious to the skilled man seeking to improve the VR-2332 vaccine virus.

The Opposition Division decided it was not obvious to the skilled man – but only because the skilled man had no incentive to improve attenuation. In actuality, the skilled man had no reason to expect that D1 was perfectly attenuated (there being no data) and the skilled man always has incentive to seek improvements.

Moreover, the skilled man would have repeated D1 to determine how efficacious the vaccine was against PRRS. In paragraph 10 of his Declaration, Prof. Murtaugh says that the virus of D1 "has virulence and pathogenesis properties that are unsuitable for a vaccine." If this is the case, the skilled man, upon obtaining a sample of the virus ATCC-VR2332, and repeating the passaging sequence of the Example of D1, would have found that the attenuated virus was insufficiently attenuated for commercialization. Faced with this problem, (as was the case in D10 discussed below) – the skilled man would have continued the attenuation process by further passaging.

Passaging to improve attenuation is an obvious and commonly used technique to attenuate. There is no prejudice to attenuating by passaging beyond the number of passages in D1.

Moreover, as explained above RespPRRS®, Ingelvac MLV was marketed prior to the priority date of the Patent and the attenuated live vaccine virus was available for the skilled man to sequence and determine its properties. Even if the availability of the product does not explicitly disclose the method by which it is obtained, the route taken by the Patentee to obtain the vaccine virus is entirely obvious.

In addition to D1, D15 relates to vaccines against PRRS which are attenuated or inactivated vaccines. The particular PRRS isolate disclosed in D15 is I-1140, but the description states on page 6, second paragraph that "*the present vaccine can be prepared from both the Isolate no. 10 deposited with the CNCM under no. I-1140 and from any other available or isolatable PRRS virus isolates.*" and page 9, first sentence, "*although a vaccine according to the invention may be derived from any PRRS virus isolate.*". Furthermore, on page 7, 3rd paragraph, it is disclosed that the production of the live attenuated virus vaccine is "for example, by 10-200 passages

in eggs or such cultures" [emphasis added] where the cultures includes susceptible tissue cells.

Therefore, D15 teaches that any PRRS isolate can be attenuated by multiple passaging in susceptible tissue cells and indicates that a range of 10 to 200 passages would be quite usual.

This is further supported by a post published document D10 (published 7-10 July 1996, i.e., prior to the A1 publication of the Patent) where USDA researchers compare RespPRRS® vaccine virus with their own PRRS virus isolates. D10 shows that the USDA PRRS virus isolates were much more virulent at the 84$^{th}$ passage than RespPRRS® vaccine virus, and needed much higher levels of attenuation such that the author was undertaking studies to evaluate the 250$^{th}$ cell culture passage for those isolates. D10 illustrates that at a time contemporaneous with the priority date of the Patent, the skilled man was motivated to use high numbers of passages to improve the clinical efficacy and safety of PRRS virus isolate.

Therefore, the skilled man considering how to improve the vaccine of D1 would certainly carry out further passaging. D1 alone, or with the skilled man's common general knowledge as demonstrated by D10, is sufficient to render the solution obvious. D1 in view of D15 also renders the solution obvious. D15 also provides the method of the Auxiliary Request except for the specific 70+ passages in MA-104 cells. That such attenuation methods were clearly within the skill of the art is further demonstrated by a very similar disclosure in D14 (see pages 6-7 and the paragraph bridging the pages, wherein it is disclosed that "in the preparation of a modified live or attenuated vaccine ...alteration of the virus ...[is accomplished] by passaging it through a non-host cell ... MA-104."

Finally, in the Summons to Oral Hearing, the Opposition Division indicated that the skilled man would be deterred from further passaging by the possibility of mutations arising which adversely affected the characteristics of the virus. This prejudice was justified by the decision on a different virus – canine coronavirus – given in T997/93. D15 and D10 show clearly that this prejudice did not exist in the art relevant to PRRS.

Thus, the method of claim 1 of Auxiliary Request 1 on which the Opposition Division decided to maintain the Patent lacks inventive step because the feature of passaging at least 70 times in MA-104 cells does not solve the technical problem as posed by the Opposition Division. In addition, with respect to the closest prior art D1, the skilled man had every reason to continue the passaging of VR-2332 in MA-104 cells to a point at which a vaccine virus which is safe and effective is achieved, this being an art recognized method of attenuating live virus PRRS vaccines.

In Summary, the Patent should be revoked in its entirety. The claims of Auxiliary Request 1 either lack novelty in view of RespPRRS®, Ingelvac MLV or lack inventive step over the Patentee's earlier patent D1, taken alone or in combination with RespPRRS®, Ingelvac MLV, or in combination with D15 or in combination with the common general knowledge of the skilled man in relation to using passaging in MA-104 cells for PRRS viruses for attenuation purposes.